perform an ophthalmological procedure on the subject to detect presence of drusen; and

detecting one or more genotypic or phenotypic markers for macular degeneration [in the eye, wherein said marker is indicative of];

whereby the subject is diagnosed to have an arterial wall disruptive disorder or [of] a predisposition to developing an arterial wall disruptive disorder.

36. (Twice Amended) A method for diagnosing, or detecting a predisposition to developing, an arterial wall disruptive disorder in a subject, comprising:

perform a radiological or anatomically targeted procedure on the subject to detect a symptom indicative of arterial wall disruptive disorder;

perform an ophthalmological procedure on the subject to detect presence of drusen; and

performing an immunoassay on a sample obtained from said subject [using an antibody specific for] to detect a gene product indicative of macular degeneration;

whereby the subject is diagnosed to have [,wherein detection of the presence of bound antibody indicates that the subject has macular degeneration or a predisposition to developing macular degeneration and therefore has] an arterial wall disruptive disorder or a predisposition to developing an arterial wall disruptive disorder.

REMARKS

Status of the Application and the Present Response

Claims 1-67 are pending in the application, with claims 8, 11, 13-18, 20-35, and 38-66 being withdrawn by the Examiner from consideration as directed to non-elected inventions. Claims 1-7, 9, 10, 12, 19, 36, 37, and 67 were examined and rejected in the instant Office Action.

With entry of this Response, claims 37 and 67 have been canceled without prejudice. Claims 1 and 36 have been amended to improve clarity. Claims 1 and 36 have also been amended to recite "perform a radiological or anatomically targeted procedure on the subject to detect a symptom indicative of arterial wall disruptive disorder" and "perform an ophthalmological procedure on the subject to detect presence of drusen." Support for the amendments is provided throughout the specification, e.g., at page 3, lines 30-32; page 54, lines 32-33; and page 55, lines 7-14. No new matter has been added by the amendments.

The following remarks address issues raised in the Office Action.

Objection to the Specification

The Examiner objected to the specification on the ground that page numbering of the specification is not continuous in Arabic numbers. In response, Applicant expresses his intention to correct any informalities of the specification, e.g., by providing a substitute specification, upon a notice of allowable subject matter in the subject application.

Rejection under 35 U.S.C. 112, 1st Paragraph

Claims 1-7, 9, 10, 12, 19, 36, 37, and 67 were rejected as allegedly not enabled. A number of grounds have been advanced to support the rejections. Specifically, referring to the correlation between aneurysm and AMD discovered by the present inventor, the Office Action asserted that the specification fails to teach whether such co-incidence is significant over other influential risk factors. In addition, the Office Action was of the view that the subject specification does not teach the elastin levels in groups of individuals having AMD+/AAA+ and AMD-/AAA+ to establish a relationship between the markers and the diseases. The Office Action further faulted the present invention on the ground that the number of AMD cases disclosed in Example 1 is too small to be representative of the entire population of AMD. The Office Action also questioned that the subject application showed increased elastin mRNA levels in AMD/AAA patients while histological findings from prior art reported reduced elastin presence. In conclusion, the Examiner stated that the present

disclosure only represents "an initial investigation into the feasibility" of developing a useful diagnosis, and is therefore not enabled.

Applicant respectfully traverses the rejections. Nevertheless, to expedite prosecution, Applicant has canceled claims 37 and 67 without prejudice. Applicant has also amended independent claims 1 and 36. The amended claims now recite additional steps of performing a traditional diagnostic procedure for arterial wall disruptive disorder and performing an ophthalmological procedure for the presence of drusen.

The presently claimed invention is undoubtedly enabled. The procedures recited in the newly added claim elements are all well known in the art and hence enabled. Detection of a genotypic or phenotypic markers for macular degeneration is taught throughout the specification. Therefore, the skilled artisan can readily practice the presently claimed invention based on the present disclosure and knowledge known in the art. In addition, using the presently claimed invention, there is no doubt that one would be able to diagnose in a subject an arterial wall disruptive disorder or a predisposition to develop an arterial wall disruptive disorder. Other than performing a traditional procedure for diagnosing aneurysms, the present invention additionally calls for the detection of drusen and the presence of an additional genotypic or phenotypic marker for macular degeneration. The latter results simply provide additional evidence that the subject has aneurysm or a predisposition to develop aneurysm.

As demonstrated by the present inventor, genotypic or phenotypic markers for macular degeneration indeed have diagnostic value in detecting arterial wall disruptive disorders. Contrary to the assertions made in the Office Action, the specification has provided ample evidence substantiating the correlation between macular degeneration and arterial wall disruptive disorders (see, e.g., summary at pages 67-68). The evidence includes (but is not limited to): 1) a strong statistical correlation between AAA and neovascular AMD ($P<0.00001$) has been documented in a large repository of human donor eyes; 2) in a small clinical trial, five out of eight patients with AAA were diagnosed with a characteristic AAA fundus phenotype and AMD when examined ophthalmoscopically; 3) a review of patients seen at the University

of Iowa over the past five years for both AAA and AMD reveals a similar AAA fundus phenotype; 4) rigorous histochemical and biochemical analyses of drusen have revealed that drusen and arterial disease plaques are similar in composition; 5) a novel association between drusen and dendritic cells has been identified; 6) ultrastructural and immunohistochemical examination of choroids from 151 human has revealed a novel pathology associated with these conditions; 7) RT-PCR analyses of RPE-choroid complexes have revealed distinct patterns of up- and down-regulated gene expression between the two groups; 8) autoantibodies directed against two specific RPE-, retina- (approximately 35kDa and 50kDa), and drusen-associated (approximately 42kDa) proteins have been identified in the sera of patients with both AMD and AAA; and 9) gene array analyses of RPE/choroid tissues derived from human donors with AMD and/or AAA have provided compelling evidence for shared mechanisms of pathogenesis (gene expression profiles) between these disorders.

Applicant further notes that the legal standard for judging whether disclosed data is sufficient to satisfy the enablement requirement of 35 U.S.C. 112, first paragraph, is whether one of skill in the art would accept the data as reasonably correlating to the asserted claims. A rigorous or an invariable exact correlation is not required. In view of the present disclosure, e.g., as outlined above, Applicant respectfully submits that the required correlation is clearly present in the instant case.

Finally, the Office Action suggested that there appears to be inconsistency between the present disclosure and the prior art regarding elastin levels in macular degeneration and/or aneurysm patients. In response, Applicant notes that the specification only indicates increased elastin mRNA levels in the liver of AMD/AAA patients. By contrast, the histochemical studies reported in the prior art (e.g., Satta et al.) at most suggested degradation of elastin in situ in aorta or aneurysm tissue. For example, Satta et al., employing a monoclonal anti-elastin BA-4 antibody, at most demonstrated decreased prevalence of the elastin epitope recognized by this specific antibody, and therefore suggested elastin degradation in the tissues. By no means did Satta et al. indicate that elastin protein expression levels in these tissues are reduced. Further, even assuming that the prior art indeed suggested a

decreased elastin expression level in the vascular tissue, it still does not follow that elastin mRNA levels in liver would necessarily have also decreased. Thus, there is no inconsistency between the present disclosure and the prior art teachings.

In view of the above amendments and remarks, Applicant respectfully submits that the presently claimed invention is enabled. Withdrawal of the instant rejections is accordingly requested.

Rejection under 35 U.S.C. 112, 2nd Paragraph

Claims 1-7, 9, 10, 12, 19, 36, 37, and 67 were also rejected under 35 U.S.C. 112, 2nd paragraph, based on alleged indefiniteness. Specifically, claims 1-7, 9, 10, 12, 19, 36 were rejected as allegedly incomplete. Claims 37 and 67 were rejected on the ground it is not clear what components are included or excluded in the claimed kits.

While Applicant respectfully traverses the rejections, Applicant has canceled amended claims 1 and 36. The amended claims now clearly relate back to the preamble. In addition, claims 37 and 67 have been canceled, which moot the rejection of these two claims. Accordingly, the instant rejections should be withdrawn.

Rejections Under 35 U.S.C. 102

Claims 1, 2, 4, 6, 7, 9, 10, 36, 37, and 67 were rejected under 35 U.S.C. 102(a) as allegedly anticipated by Satta et al. (Eur. J. Vasc. Endovasc. Surg. 15:313-9, 1998). Claims 1, 2, 6, 7, 9, 10, 36, 37, and 67 were also rejected as allegedly anticipated by Juvonen et al. (Eur. J. Vasc. Surg. 8: 70-7, 1994).

As noted above, Applicant has canceled claims 37 and 67 in an effort to further expedite prosecution of the subject application. The other independent claims, claims 1 and 36, have been amended to recite additional steps. These steps include performing a traditional diagnostic procedure for arterial wall disruptive disorder and performing an ophthalmological procedure for the presence of drusen.

Satta et al. reported observation of inflammation and elastin degradation in abdominal aortic aneurysm disease. Juvonen et al. discussed a study on segmental mediolytic arteritis by electronmicroscopic and immunohistochemical techniques. Clearly, neither Satta et al. nor Juvonen et al. taught examining the same subject for presence of drusen and other genotypic/phenotypic markers indicative of macular degeneration, as well as symptoms of arterial wall disruptive disorders. Therefore, claims 1 and 36, as well as dependent claims 2, 4, 6, 7, 9, 10, are novel over the cited art. Accordingly, Applicant respectfully requests that the instant rejections be withdrawn.

Rejection of Under 35 U.S.C. 103

Claims 1-7, 9, 10, 36, 37, and 67 were further rejected as allegedly obvious over Satta et al. and/or Juvonen et al. in view of the discussion of aneurysm in Encyclopædia Britanica.

In response, Applicant notes that claims 37 and 67 have been canceled without prejudice. In addition, as discussed above, independent claims 1 and 36 have been amended which now recite performing additional diagnostic procedures for the presence of drusen and symptoms of arterial wall disruptive disorder. Further, it is to be noted that was the present inventor who discovered the genotypic and phenotypic correlation between macular degeneration and arterial wall disruptive disorders.

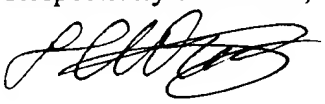
On the other hand, neither Satta et al. nor Juvonen et al., the primary references cited for the instant rejection, taught or suggested examination of the same subject with conventional diagnostic procedures for the presence of drusen and for symptoms of aneurysms. As for the Encyclopædia Britanica reference, it is merely a brief description of aneurysm. It does not discuss methods for diagnosis of aneurysms, let alone employment of combined procedures for detecting drusen and diagnosing aneurysms. Thus, the cited references do not teach or suggest all the elements of the presently claimed invention. For at least this reason, Applicant submits that the present invention is nonobvious over the cited art and respectfully requests withdrawal of the rejections under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400 x 5209.

Respectfully submitted,



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Appendix: Clean version of all claims under consideration

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